INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/DE 98/03818

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12Q1/68 C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIGGETT S.: "Polymorphisms of the beta-2 adrenergic receptor and asthma" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, vol. 156, no. 4, October 1997, pages S156-S162, XP002106240 siehe insbes. Abb. 1	1,2

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 1999	30/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kania, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/03818

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HALL I.: "Beta-2 adrenoceptor polymorphisms: are they clinically important ?" THORAX, vol. 51, 1996, pages 351-353, XP002106246 see the whole document	1-33
P,X	TIMMERMANN B ET AL: "Novel DNA sequence differences in the beta2 - adrenergic receptor gene promoter region." HUMAN MUTATION, (1998) 11 (4) 343-4. JOURNAL CODE: BRD. ISSN: 1059-7794., XP002106247 United States see abstract	1-8
P,X	TIMMERMANN B. ET AL: ".beta.-2 Adrenoceptor genetic variation is associated with genetic predisposition to essential hypertension: The Bergen Blood Pressure Study" KIDNEY INTERNATIONAL, (1998) 53/6 (1455-1460). REFS: 32 ISSN: 0085-2538 CODEN: KDYIA5, XP002106248 United States see the whole document	1-33
P,X	MCGRAW D W ET AL: "Polymorphisms of the 5' leader cistron of the human beta2 - adrenergic receptor regulate receptor expression." JOURNAL OF CLINICAL INVESTIGATION, (1998 DEC 1) 102 (11) 1927-32. JOURNAL CODE: HS7. ISSN: 0021-9738., XP002106249 United States see the whole document	1-33
T	SCOTT M G ET AL: "Identification of novel polymorphisms within the promoter region of the human beta2 adrenergic receptor gene." BRITISH JOURNAL OF PHARMACOLOGY, (1999 FEB) 126 (4) 841-4. JOURNAL CODE: BOO. ISSN: 0007-1188., XP002106250 ENGLAND: United Kingdom see the whole document	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 98/03818

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	TURKI J ET AL: "Myocardial signaling defects and impaired cardiac function of a human beta 2 - adrenergic receptor polymorphism expressed in transgenic mice." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 SEP 17) 93 (19) 10483-8. JOURNAL CODE: PV3. ISSN: 0027-8424., XP002106241 United States see the whole document ---	1,2,33
X	TURKI J. ET AL.: "GENETIC POLYMORPHISMS OF THE BETA2-ADRENERGIC RECEPTOR IN NOCTURNAL AND NONNOCTURNAL ASTHMA" JOURNAL OF CLINICAL INVESTIGATION, vol. 95, 1995, pages 1635-1641, XP002106242 see the whole document ---	1,2,9, 10, 17-21, 24,26, 27,29, 31-33
X	LARGE V. ET AL.: "Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function" JOURNAL OF CLINICAL INVESTIGATION, vol. 100, no. 12, 1997, pages 3005-3013, XP002106243 see the whole document ---	1,2,9, 17,18, 22,24, 26,31
A	PAROLA A L ET AL: "The peptide product of a 5' leader cistron in the beta 2 adrenergic receptor mRNA inhibits receptor synthesis." JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 FEB 11) 269 (6) 4497-505. JOURNAL CODE: HIV. ISSN: 0021-9258., XP002106244 United States cited in the application siehe insbes. Abb. 2 ---	1-33
A	KOBILKA B K ET AL: "Functional activity and regulation of human beta 2 - adrenergic receptors expressed in Xenopus oocytes." JOURNAL OF BIOLOGICAL CHEMISTRY, (1987 NOV 15) 262 (32) 15796-802. JOURNAL CODE: HIV. ISSN: 0021-9258., XP002106245 United States cited in the application see the whole document --- -/--	1-33

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/DE 98/03818

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C12N15/12 C12Q1/68 C07K14/705

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C07K C12N C12Q

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	LIGGETT S.: "Polymorphisms of the beta-2 adrenergic receptor and asthma" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, Bd. 156, Nr. 4, Oktober 1997, Seiten S156-S162, XP002106240 siehe insbes. Abb. 1	1,2

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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[ ] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
17. Juni 1999	30/06/1999

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kania, T

1

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	TURKI J ET AL: "Myocardial signaling defects and impaired cardiac function of a human beta 2 - adrenergic receptor polymorphism expressed in transgenic mice." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 SEP 17) 93 (19) 10483-8. JOURNAL CODE: PV3. ISSN: 0027-8424., XP002106241 United States siehe das ganze Dokument	1,2,33
X	TURKI J. ET AL.: "GENETIC POLYMORPHISMS OF THE BETA2-ADRENERGIC RECEPTOR IN NOCTURNAL AND NONNOCTURNAL ASTHMA" JOURNAL OF CLINICAL INVESTIGATION, Bd. 95, 1995, Seiten 1635-1641, XP002106242 siehe das ganze Dokument	1,2,9, 10, 17-21, 24,26, 27,29, 31-33
X	LARGE V. ET AL.: "Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function" JOURNAL OF CLINICAL INVESTIGATION, Bd. 100, Nr. 12, 1997, Seiten 3005-3013, XP002106243 siehe das ganze Dokument	1,2,9, 17,18, 22,24, 26,31
A	PAROLA A L ET AL: "The peptide product of a 5' leader cistron in the beta 2 adrenergic receptor mRNA inhibits receptor synthesis." JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 FEB 11) 269 (6) 4497-505. JOURNAL CODE: HIV. ISSN: 0021-9258., XP002106244 United States in der Anmeldung erwähnt siehe insbes. Abb. 2	1-33
A	KOBILKA B K ET AL: "Functional activity and regulation of human beta 2 - adrenergic receptors expressed in Xenopus oocytes." JOURNAL OF BIOLOGICAL CHEMISTRY, (1987 NOV 15) 262 (32) 15796-802. JOURNAL CODE: HIV. ISSN: 0021-9258., XP002106245 United States in der Anmeldung erwähnt siehe das ganze Dokument	1-33

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INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/US99/27963

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8, 11 and 13-27

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/27963

Continuation of Item 4 of the first sheet:

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I, claim(s) 1-4, 6, 7, 11, 13 and 16-27, drawn to drawn to a method of genotyping beta 2-adrenergic receptor.

Group II, claim(s) 9,10 and 12, drawn to a method of detecting peptide variants.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature of group I is a method for genotyping the beta 2-adrenergic receptor. Group II is drawn to a method of detecting peptide variants of the receptor using antibodies. The prior art discloses a method of determining genetic polymorphism in the beta 2-adrenergic receptor (Turki et al. Journal of Clinical Investigation 1995 Vol 95 pages 1653-1641). Therefore, groups I and II lack a special technical feature.

Continuation of B. FIELDS SEARCHED Item 3: WEST, Medline, Biosis
beta adrenergic receptor, adrenergic receptor, polymorphism, genotype, haplotype

AMENDED CLAIMS

[received by the International Bureau on 25 May 2000 (25.05.00);
original claim 16 amended; remaining claims unchanged (1 page)]

(a) isolating from the individual a nucleic acid molecule containing only one of the two copies of the β_2AR gene, or a fragment thereof, that is present in the individual; and

(b) determining in that copy the identity of the nucleotide at the 5' LC PS and at one or more additional β_2AR polymorphic sites.

17. The method of claim 16, wherein the additional polymorphic sites are selected from the group consisting of -20PS, +46PS, +79PS, +100PS and +491PS.

18. A method for predicting an individual's genotype for at least one coding block polymorphic site (cb PS) in the β_2-adrenergic receptor gene, which comprises determining the individual's genotype for the 5′ leader cistron polymorphic site (5′LC PS) and assigning a genotype for the cb PS which is consistent with the individual's 5′LC PS genotype, wherein the cb PS is selected from the group consisting of +46PS and +79PS.

19. A method for determining the frequency of a β_2AR genotype or haplotype in a population, comprising

(a) determining the genotype or the haplotype pair for the β_2AR 5′ gene that is present in each member of the population and

(b) calculating the frequency any particular β_2AR genotype or haplotype is found in the population.

20. The method of claim 19, wherein the population is a trait population and the trait is selected from the group consisting of congestive heart failure, ischemic heart disease arrhythmia, hypertension, migraine asthma, chronic obstructive pulmonary disease (COPD), anaphylaxis, obesity, diabetes and premature labor.

21. A method for identifying an association between a polymorphism in the β_2AR 5′ leader cistron and a trait, which comprises comparing the frequency of the polymorphism in a population exhibiting the trait with the frequency of the polymorphism in a reference population, wherein a higher frequency of the polymorphism in the trait population than in the reference population indicates the polymorphism is associated with the trait.

(a) isolating from the individual a nucleic acid molecule containing only one of the two copies of the β_2AR gene, or a fragment thereof, that is present in the individual; and

(b) determining the identity of the nucleotide at two or more additional polymorphic sites.

17. The method of claim 16, wherein the additional polymorphic sites are selected from the group consisting of -20PS, +46PS, +79PS, +100PS and +491PS.

18. A method for predicting an individual's genotype for at least one coding block polymorphic site (cb PS) in the β_2-adrenergic receptor gene, which comprises determining the individual's genotype for the 5′ leader cistron polymorphic site (5′LC PS) and assigning a genotype for the cb PS which is consistent with the individual's 5′LC PS genotype, wherein the cb PS is selected from the group consisting of +46PS and +79PS.

19. A method for determining the frequency of a β_2AR genotype or haplotype in a population, comprising

(a) determining the genotype or the haplotype pair for the β_2AR 5′ gene that is present in each member of the population and

(b) calculating the frequency any particular β_2AR genotype or haplotype is found in the population.

20. The method of claim 19, wherein the population is a trait population and the trait is selected from the group consisting of congestive heart failure, ischemic heart disease arrhythmia, hypertension, migraine asthma, chronic obstructive pulmonary disease (COPD), anaphylaxis, obesity, diabetes and premature labor.

21. A method for identifying an association between a polymorphism in the β_2AR 5′ leader cistron and a trait, which comprises comparing the frequency of the polymorphism in a population exhibiting the trait with the frequency of the polymorphism in a reference population, wherein a higher frequency of the polymorphism in the trait population than in the reference population indicates the polymorphism is associated with the trait.

PATENT COOPERATION TREATY

PCT

REC'D 09 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16570-2265	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/27963	International filing date *(day/month/year)* 24 November 1999 (24.11.1999)	Priority date *(day/month/year)* 25 November 1998 (25.11.1998)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68 and US Cl.: 435/6		
Applicant UNIVERSITY OF CINCINNATI		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 May 2000 (01.05.2000)	23 FEBRUARY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99[illegible]3

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-35 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 36, 37 and 39, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 38, filed with the letter of 01 May 2000 (01.05.2000).

☒ the drawings:
pages 1-8, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMI[illegible]Y EXAMINATION REPORT

International applicat[illegible]No.
PCT/US9[illegible]63

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-8, 11, 13-27	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-8, 11, 13-18 and 21-27	YES
	Claims 19 and 20	NO
Industrial Applicability (IA)	Claims 1-8, 11 and 13-27	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 19 and 20 lack an inventive step under PCT Article 33(3) as being obvious over Ligget S.B. (American Journal of Respiratory Critical Care Medicine 1997) in view of Turki et al. (Proceeding of the National Academy of Science 1996). The instant invention is directed to haplotyping the ß-2 AR 5'-adrenergic receptor gene and correlating the polymorphisms with a disease state. By the definition given in the specification a gene includes information for the regulated biosynthesis of RNA including introns. It is not clear where the starting point for the 5'gene is and because introns are included by definition as being part of the gene, any reference able to detect genomic DNA of the receptor would meet the criteria of the claims. Unless the claims are limited to the 5' gene comprising the 5' leader cistron polymorphic site the following art rejection applies. Ligget et al. discloses methods of obtaining nucleic acids for diagnosis from patients using cells from blood, urine, saliva or tissue samples. The genomic DNA may be used directly for analysis or it may be amplified using PCR. The DNA product may then be assessed for the presence of mutations by several methods including allele-specific hybridization, allele-specific PCR, temperature gradient gel electrophoresis and direct sequencing. Ligget et al. discloses a method of correlating the asthmatic phenotype with the polymorphism the gene of the beta-2-adrenergic receptor (see table 1 and 2). Ligget et al. specifically discloses the polymorphic sites at +46PS, +79PS, +100 PS and +491PS. The reference does not suggest correlating the polymorphism of the beta-2 adrenergic receptor with another phenotype. Turki et al. teach polymorphism in the beta-2 adrenergic receptor in myocardial signaling defects. It would have been obvious to one of ordinary skill at the time the invention made to apply the techniques of Ligget et al. with the analysis taught by Turki et al. to correlate differences in the receptor to varying disease states. Therefore, the instant invention is obvious over Ligget S.B. in view of Turki et al.

Claims 1-8, 11, 13-18 and 21-27 mee the criteria set out under PCT Article 33(2) and 33(3) The art does not disclose or suggest genotyping the beta-2-adrenergic receptor in the 5' leader cistron and correlating polymorphism in this region with disease. While the cited prior art discloses a primer that comprises SEQ ID:5 (Lenzen et al. WO 97/35973), the art does not suggest using this primer as a probe for genotyping the DNA from the 5' leader cistron of the beta-2 adrenergic receptor and correlating polymorphisms with a disease state. Therefore, the subject matter of claims 1-8, 11, 13-18 and 21-27 appears to be both novel and inventive over the documents cited in the international search report. Thus, these claims appear to meet the requirements of PCT Articles 33(2) and (3).

Claims 1-8, 11 and 13-27 meet the criteria of PCT Article 33 (4), because the instant invention has industrial applicability.

---------- NEW CITATIONS ----------

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 19 is objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph. It is not clear what is meant by "ß2-AR 5' gene", specifically it is not clear where the staring point of the 5' gene is located. The definition of the gene includes introns as part of the segment of DNA necessary for regulated RNA synthesis. Therefore, it is uncertain if the 5' gene region refers to any region located 5' of any exon. This lack of clarity can be removed by limiting the 5' gene to the 5' leader cistron polymorphic site, or indicating that the 5'-gene are those regions that are part of the 5'untranslated region located 5' of the translation start site.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
International application No. PCT/US99/27963	**Applicant's or agent's file reference** 16570-2265
International filing date (day/month/year) 24 November 1999 (24.11.99)	**Priority date** (day/month/year) 25 November 1998 (25.11.98)
Applicant LIGGETT, Stephen, B.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 May 2000 (01.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12Q 1/68

A1

(11) International Publication Number: **WO 00/31307**

(43) International Publication Date: 2 June 2000 (02.06.00)

(21) International Application Number: PCT/US99/27963

(22) International Filing Date: 24 November 1999 (24.11.99)

(30) Priority Data:
60/109,886 25 November 1998 (25.11.98) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: POLYMORPHISMS IN THE 5' LEADER CISTRON OF THE β_2–ADRENERGIC RECEPTOR

(57) Abstract

A novel polymorphic site in the 5' leader cistron of the β_2–adrenergic receptor (β_2AR) gene is disclosed. The polymorphisms present at this site result in different levels of inhibition of translation of β_2AR mRNA. Compositions and methods for genotyping this polymorphic site are disclosed. In addition, methods for using this genotype information are disclosed, including predicting genetic predisposition to a disease modified by β_2AR expression and predicting a patient's bronchodilating response to β_2–agonists.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/27963

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68
US CL : 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6, 91.2; 530/350; 536/24.1, 24.3, 24.33

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	TURKI et al. Genetic polymorphisms of the beta2-adrenergic receptor in nocturnal and nonnocturnal asthma: evidence that Gly16 correlates with the nocturnal phenotype. Journal of Clinical Investigation 1995, Vol. 95, pages 1635-1641, especially table 1.	16-19 --- 1-4,6,7, 11, 13, 21, 23, 24, 26, 27
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Y	US 5,817,477 (SOPPET et al.) 06 October 1998 (06.10.1998), see column 15-18.	1-4, 6, 7, 11, 13, 16, 18
Y	US 5,589,331 (NIELSEN et al.) 31 December 1996 (31.12.1996), see columns 6-9.	1-4, 6, 7, 11, 13, 16, 18, 19-22, 24-26
X	WO 97/35973 (CABINET ORES) 02 October 1997 (02.10.97), SEQ ID 27.	5, 14
Y	US 5,700,907 (HERCEND et al.) 23 December 1997 (23.12.99), SEQ ID 21.	8, 15
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Date of the actual completion of the international search	Date of mailing of the international search report
01 February 2000 (01.02.2000)	06 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Ulrike Winkler, Ph.D. Telephone No. 703-308-0196

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/DE 98/03818

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	HALL I.: "Beta-2 adrenoceptor polymorphisms: are they clinically important ?" THORAX, Bd. 51, 1996, Seiten 351-353, XP002106246 siehe das ganze Dokument	1-33
P,X	TIMMERMANN B ET AL: "Novel DNA sequence differences in the beta2 - adrenergic receptor gene promoter region." HUMAN MUTATION, (1998) 11 (4) 343-4. JOURNAL CODE: BRD. ISSN: 1059-7794., XP002106247 United States siehe Zusammenfassung	1-8
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T	SCOTT M G ET AL: "Identification of novel polymorphisms within the promoter region of the human beta2 adrenergic receptor gene." BRITISH JOURNAL OF PHARMACOLOGY, (1999 FEB) 126 (4) 841-4. JOURNAL CODE: BOO. ISSN: 0007-1188., XP002106250 ENGLAND: United Kingdom siehe das ganze Dokument	1-33